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<p>(21) International Application Number: PCT/NL97/00531</p> <p>(22) International Filing Date: 23 September 1997 (23.09.97)</p> <p>(30) Priority Data: 9600805 24 September 1996 (24.09.96) BI</p> <p>(71) Applicant (for all designated States except US): DSM N.V. [NL/NL]; Het Overloon 1, NL-6411 TE Heerlen (NL).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): BOONEN, Jozef, Johannes, Catharina, Jacobus [NL/NL]; De Soom 3, NL-5971 MA Grubbenvorst (NL).</p> <p>(74) Agent: JACOBS, Monique, Sophie, Nicole; Octrooibureau DSM, P.O. Box 9, NL-6160 MA Geleen (NL).</p>		<p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: PROCESS FOR THE PREPARATION OF AN INORGANIC SALT OF AN OPTICALLY ACTIVE PHENYLGLYCINE DERIVATIVE</p> <p>(57) Abstract</p> <p>Process for the preparation of an inorganic salt of an optically active phenylglycine derivative, in which a diastereoisomeric salt of the optically active phenylglycine derivative and an optically active acid is treated with a strong inorganic acid, in which at least a portion of the strong inorganic acid is added to a mixture containing an amount of the diastereoisomeric salt as a solid substance. The process according to the invention can be used with particular advantage in the preparation of an optically active phenylglycine derivative via an asymmetric transformation in which the reaction mixture obtained after the asymmetric transformation is treated with a strong inorganic acid without the formed, precipitated diastereoisomeric salt of the optically active phenylglycine derivative and the optically active acid being isolated and dissolved beforehand.</p>		

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5 PROCESS FOR THE PREPARATION OF AN INORGANIC SALT OF AN
 OPTICALLY ACTIVE PHENYLGLYCINE DERIVATIVE

 The invention relates to a process for the
preparation of an inorganic salt of an optically active
10 phenylglycine derivative in which a diastereoisomeric
salt of the optically active phenylglycine derivative
and an optically active acid is treated with a strong
inorganic acid, characterised in that at least a
portion of the strong inorganic acid is added to a
15 mixture containing an amount of the diastereoisomeric
salt as a solid substance.

 Such a process is described in EP-A-442584,
in which the L-mandelic acid salt of D-
phenylglycineamide (D-PGA), after an asymmetric
20 transformation reaction, is filtered off from the
reaction mixture, washed and subsequently dissolved in
water and converted into the D-PGA HCl salt with the
aid of HCl.

 The known process for converting the mandelic
25 acid salt of D-PGA into the D-PGA.HCl salt is very
complex and involves substantial losses of D-PGA and L-
mandelic acid.

 The aim of the invention is to provide a
process that does not present the above drawbacks.

30 This is achieved according to the invention
by adding at least a portion of the strong inorganic
acid to a reaction mixture containing an amount of the
diastereoisomeric salt as a solid substance.

 Surprisingly, it has been found that it is
35 possible to realize full conversion of the
diastereoisomeric salt of the phenylglycine derivative

and the optically active acid into the inorganic salt of the optically active phenylglycine derivative without isolation and/or dissolution of the diastereoisomeric salt and with the optical activity, to be expressed in enantiomeric excess (e.e.) being retained.

Asymmetric transformations in which one enantiomer is isolated from a racemic mixture and the other enantiomer is racemized in situ are known in the literature and are described in for example the aforementioned patent application EP-A-442584. For a commercially attractive process an efficient recovery of both the optically active phenylglycine derivative and the optically active acid is however of great importance. The known methods for the recovery of the optically active enantiomer and the optically active acid are complex, however. For example, in EP-A-442584 the optically active phenylglycine derivative is obtained from the isolated diastereoisomeric salt by dissolving the salt in a mixture of water and an almost equimolar amount of mineral acid such as hydrochloric acid, sulphuric acid, nitric acid or phosphoric acid and extracting the optically active carboxylic acid with the aid of an extractive-distillation agent. This process is rather laborious; it moreover often involves the loss of a significant portion of the optically active acid.

The process according to the invention can with particular advantage be applied to the reaction mixture obtained after the asymmetric transformation. The invention hence also relates to a process for the preparation of an optically active phenylglycine derivative in which the reaction mixture obtained after the asymmetric transformation is treated with a strong inorganic acid without the formed, precipitated diastereoisomeric salt of the optically active phenylglycine derivative and the optically active acid

being isolated and dissolved beforehand.

Preferably, the amide or an ester of a phenylglycine is used as the phenylglycine derivative, which phenylglycine may or may not be substituted, in particular phenylglycine or p-hydroxyphenylglycine.

As the strong inorganic acid use is preferably made of an acid having a pKa value that is greater than the pKa value of the optically active acid. Particularly suitable inorganic acids are for example mineral acids, in particular sulphuric acid or hydrochloric acid, (gaseous or in solution).

A particularly good embodiment is obtained when hydrochloric acid is used, for it has been found that the use of an equivalent amount of hydrochloric acid relative to the amount of diastereoisomeric salt results in an almost quantitative conversion. In the application of the process according to the invention to the reaction mixture obtained after an asymmetric transformation, in particular, this presents the advantage that no inorganic salt is present in the mother liquor that remains after the recovery of the phenylglycine derivative.HCl salt. As a result, the mother liquor containing the optically active acid obtained in the conversion can be returned as such to the asymmetric transformation, for it has been found that the presence of inorganic acid interferes with the asymmetric transformation reaction, in particular the racemization.

The temperature at which the treatment with the strong inorganic acid takes place is not critical and preferably lies between 0 and 125°C, in particular between 20 and 80°C. In practice, when the treatment is applied to a reaction mixture obtained after an asymmetric transformation, it will usually take place at a temperature that is the same as or lower than the temperature at which the asymmetric transformation is carried out.

The pressure at which the treatment with the strong inorganic acid takes place is not critical either and will usually lie between 0.01 and 1 MPa, in particular between 0.05 and 0.2 MPa. Preferably the treatment with the strong inorganic acid is carried out at atmospheric pressure.

Carbonyl compounds that can be used in the asymmetric transformation are for example aldehydes or ketones, in particular aromatic aldehydes such as benzaldehyde, anisealdehyde, o-, p- or m-nitrobenzaldehyde, o-, p- or m-chlorobenzaldehyde or aliphatic aldehydes such as isobutyraldehyde or isovaleraldehyde, ketones such as methylisobutylketone, butanone or acetone. The amount of carbonyl compound to be added is preferably 0.5-4.0 equivalents relative to the amount of phenylglycine derivative, in particular 1-2 equivalents.

Instead of starting from a mixture of L- and D-phenylglycine derivatives and a carbonyl compound, it is also possible to start from a mixture of the Schiff bases of L- and D-phenylglycine derivatives. In this case it is not strictly necessary to add an extra amount of carbonyl compound. In this case, in order to obtain an optimum yield of the diastereoisomeric salt of optically active phenylglycine derivative and optically active acid, an amount of water that is at least equimolar relative to the amount of Schiff base must be added. The use of less than an equimolar amount of water leads to a virtually proportional decrease in the yield.

In the asymmetric transformation use is made of optically active acids such as carboxylic acids. Suitable examples of optically active acids are mandelic acid, tartaric acid, 2-pyrrolidone-5-carboxylic acid and N-acetylphenylglycine. The acidity (pKa) will usually be between 3 and 5. The amount of optically active acid to be used may vary within a wide

range and will generally lie between 0.9 and 1.2 equivalents of optically active acid relative to the amino acid amide. Preferably, an equivalent amount of carboxylic acid is used.

5 Suitable solvents for the asymmetric transformation are for example hydrocarbons such as cyclohexane, heptane and octane, aromatic hydrocarbons such as toluene, xylene and benzene, ethers such as methyl-tertiary-butyl ether, dioxane, tetrahydrofuran
10 and anisole, esters such as butyl acetate and ethyl acetate, ketones such as acetone, butanone, methylisobutylketone, carboxylic acids, aldehydes or mixtures of these substances. It will be clear that the solvent must be chosen so that it does not enter into
15 irreversible chemical reactions with the amino acid amide, the optically active carboxylic acid or the aldehyde.

 The pressure at which the asymmetric transformation is carried out is not critical and
20 usually lies between 0.01 and 1 MPa, in particular 0.05 and 0.2 MPa. Preferably, the process is carried out at atmospheric pressure. The temperature at which the asymmetric transformation is carried out may vary within a wide range and is generally 70-120°C,
25 preferably 75-100°C, in particular 80-90°C. The reaction time is usually 1-8 hours, preferably 1-4 hours.

 The slurry concentration of the diastereoisomeric salts at the end of the reaction is
30 about 5-30 wt.%, preferably 10-20 wt.%.

 The invention will now be elucidated with reference to the following examples, without being limited thereto.

Example I

400 grams (4 mol) of methylisobutylketone,
37.5 grams (0.25 mol) of DL-phenylglycineamide and 39.9
grams (0.263 mol) of L(+) mandelic acid were stirred in
5 a reaction flask fitted with a stirrer, a thermometer
and a reflux cooler for about 2.5 hours, at a
temperature of 85°C. After cooling to 30°C, 27.6 grams
(0.25 mol) of HCl, 33% aqueous solution, was dosed to
the reaction mixture in 1 hour. The hydrochloric salt
10 of D(-)phenylglycineamide formed was filtered and
washed on the filter with 2 x 25 ml of
methylisobutylketone. After drying, 44.5 grams of
filtered product was obtained.
Yield = 95.4%
15 enantiomeric excess = 97.2 %
phenylglycineamide content (potentiometrically
determined) = 80.1% (theoretical value 80.4%)

Example II

20 180 grams (1.8 mol) of methylisobutylketone,
18.12 grams (0.10 mol) of DL-p-hydroxyphenylglycine
methyl ester and 15.2 grams (0.10 mol) of L(+)mandelic
acid were stirred in a reaction flask fitted with a
stirrer, a thermometer and a reflux cooler for 4-6
25 hours, at a temperature of 80°C. After cooling to 30°C,
9.49 ml (0.10 mol) of HCl, 33% aqueous solution, was
dosed to the reaction mixture in 1 hour. The
hydrochloric salt of D(-)p-hydroxyphenylglycine-methyl
ester formed was filtered and washed on the filter with
30 2*25 ml of methylisobutylketone. After drying, 16.3
grams of filtered D(-)-p-hydroxyphenylglycine-methyl
ester.HCl salt was obtained.
Yield = 89.9%
enantiomeric excess = 92.4%

C L A I M S

1. Process for the preparation of an inorganic salt
of an optically active phenylglycine derivative in
5 which a diastereoisomeric salt of the optically
active phenylglycine derivative and an optically
active acid is treated with a strong inorganic
acid, characterised in that at least a portion of
the strong inorganic acid is added to a mixture
10 containing an amount of the diastereoisomeric salt
as a solid substance.
2. Process according to Claim 1, in which a
phenylglycineamide or an ester of a phenylglycine
is used as the phenylglycine derivative.
- 15 3. Process according to Claim 1 or Claim 2, in which
hydrochloric acid or sulphuric acid is used as the
strong acid.
4. Process according to Claim 3, in which an almost
equivalent amount of hydrochloric acid is used as
20 the strong acid.
5. Process according to any one of Claims 1-4, in
which phenylglycineamide or p-
hydroxyphenylglycineamide is used as the
phenylglycine derivative.
- 25 6. Process according to any one of Claims 1-5, in
which the optically active acid is optically
active mandelic acid, tartaric acid, 2-
pyrrolidone-5-carboxylic acid or N-
acetylphenylglycine.
- 30 7. Process according to any one of Claims 1-6, in
which the mixture consists of the reaction mixture
obtained after an asymmetric transformation in
which a mixture of the L- and D-enantiomers of the
phenylglycine derivative is partly or entirely
35 converted into the diastereoisomeric salt in the
presence of a carbonyl compound (in a suitable
solvent), with the aid of the optically active

acid.

8. Process according to any one of Claims 1-6, in which the mixture consists of the reaction mixture obtained after an asymmetric transformation in which a mixture of the L- and D-enantiomers of a Schiff base of the phenylglycine derivative is partly or entirely converted into the diastereoisomeric salt with the aid of the optically active acid.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/97/00531

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C231/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 4 093 653 A (BOESTEN WILHELMUS H J) 6 June 1978 see the whole document ---	1-8
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Information on patent family members

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